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A farewell to didanosine: harm reduction and cost savings by eliminating use of didanosine

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Abstract

Didanosine (ddI) is a nucleoside reverse transcriptase inhibitor associated with adverse events and public health concerns which have diminished its place in clinical practice, particularly in resource-rich settings. While international guidelines do not contain ddI-containing regimens in preferred first- or second-line antiretroviral therapy (ART), there is no guidance for management of patients currently on ddI. In 2012 at least 20 countries purchased a total of $1–2 million of ddI. Drug purchase data in that year show 3.2–10.3 times higher costs for ddI compared to lamivudine (3TC). Given issues of multiple toxicities, monitoring, drug interactions, inconvenience, and virologic efficacy, as well as cost and formulary concerns, national (including resource-limited setting) ART programs should consider complete phase-out of ddI.

Keywords

Didanosine; HIV; antiretroviral therapy; reverse transcriptase inhibitors; drug toxicity; drug interactions

Commentary

Didanosine (ddI) is a nucleoside reverse transcriptase inhibitor (NRTI) first synthesized in 1964 for development as an anti-cancer agent, and was given an indication by the U.S. Food and Drug Administration (FDA) in 1991 for treatment of HIV infection.[1] It was the second approved antiretroviral (ARV) medication, following zidovudine (AZT) in 1987; since then over two dozen other ARVs have been licensed, many with less toxicity and easier dosing regimens. While initially ddI was used widely in absence of alternatives, its role in antiretroviral therapy (ART) has evolved over the past three decades. Patient-level concerns such as adverse events and pill burden, together with public health concerns including formulary complexity and costs, have diminished the place of ddI in clinical practice, particularly in resource-rich settings.

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Conflict of interest

The authors declare no conflict of interest.

From 2002 through 2006, World Health Organization (WHO) guidelines recommended ddI to be used in second-line regimens for children and adults.[2–5] In 2009, WHO issued rapid advice to support lamivudine (3TC)-containing regimens for second line instead of ddI-containing regimens, regardless of the presence or absence of 3TC in the patient's first-line regimen.[6] This was re-affirmed in the 2010 and 2013 guidelines.[7–9] The reasoning for favoring 3TC over ddI included lack of evidence for any advantage of ddI use, and its increased "complexity and cost" compared to 3TC. Potential virologic benefit of maintaining 3TC in second-line regimens was also cited, through selection or maintenance of the M184V mutation which confers resistance to 3TC and may reduce viral replicative capacity, although some uncertainty remains concerning the clinical benefit of this property.[10–12]

While the most recent WHO ART guidelines do not contain ddI-containing regimens in first- or second-line ART, there is no guidance for management of patients currently on ddI.[9] Based on international funding and supply system information, in 2012 at least 20 countries purchased a total of $1–2 million of ddI.[13,14] Because ddI is manufactured with several dosing strengths and formulations, this could represent up to 10 formulations that need to be maintained on a national formulary, complicating an already intricate field of ARVs.[14] These challenges could be averted through complete removal of ddI from national formularies and substitution with 3TC-containing regimens.

There are well-known concerns regarding ddI use which make it suboptimal for lifelong ART. Its use depletes the DNA polymerase which is critical in synthesis of mitochondrial DNA; this is one mechanism that leads to various forms of mitochondrial toxicity.[15] The FDA drug label was updated in 2002 to include Boxed Warnings regarding fatal pancreatitis and lactic acidosis; FDA also issued a safety alert in 2010 regarding non-cirrhotic portal hypertension.[1] Several studies and case series about these and other toxicities have been published.[16–20] Recommended clinical monitoring for patients on ddI includes routine retinal examination (optic neuritis and retinal depigmentation are rare but have been described), which is seldom available in resource-limited settings (RLS).[21] Use of ddI with stavudine or with alcohol consumption increases the risk of toxicity. Concurrent use of ddI and tenofovir requires a reduction of ddI dosing due to significant drug–drug interaction, and also may impair immunologic recovery.[1] To maximize ARV potency, ddI should be taken at least 1 h prior to, or 2 h following, food or other medications. This dosing schedule, as well as a lack of ddI-containing fixed-dose combinations (FDCs) leading to excess pill burden, creates barriers for patient adherence.

Additional concerns include that ddI may not actually be virologically active in most second-line patients, due to prevalence of L74V and other known resistance mutations in NRTI-experienced patients, some having been only recently discovered.[22–25] Evidence that continued use of ddI in a failing regimen may select for mutations that are associated with cross-resistance to other NRTIs, such as the Q151M complex and T69 insertion, has been described and could support discontinuation of the drug in patients currently receiving it.[26–28] These considerations should be viewed in the context of resource-limited settings using a public health approach to ART regimen selection without the benefit of patient-level genotyping.

The 2013 WHO consolidated ART guidelines now recommend the use of 3TC rather than ddI for second-line ART regimens. International purchasing data for low- and middle-income countries show that ddI is considerably more expensive than 3TC. Based on the 2012 Global Fund Price & Quality Reporting System, the additional per-patient direct drug cost of ddI compared to single-drug preparations of 3TC ranges from US$74 to US$223/child/year and $136 to $253/adult/year, depending on weight-adjusted dosing[13] (Figure 1). This equates to 3.2–10.3 times higher costs for ddI compared to 3TC. Per-patient prices can be significantly reduced through FDCs, especially for generic ARVs. Cost savings of using 3TC could therefore be even higher.

An argument could be made that there are relatively few patients who currently take ddI-containing regimens and a program-level phase-out would not be worth the effort. However, the disadvantages of continued ddI use, as described above, add weight to the value of a phase-out. Other than short-term programmatic effort to implement this change, the disadvantages of switching patients on ddI-containing regimens to 3TC-containing regimens are negligible. In the case of ddI and its role in second-line ART, switching to 3TC is sensible regardless of current viral suppression, ddI resistance mutations, or 3TC resistance mutations. While mutations associated with 3TC resistance, such as M184V, are quite common in treatment-experienced patients, just as for new second-line patients being maintained on 3TC per WHO guidelines, these patients likely can still benefit from its continuation.

For these reasons, it appears that all patients on ddI could benefit from a single drug substitution to 3TC-containing regimens. National ART programs, with their partners and supply chain experts, should consider whether the update of their national guidelines might include phase-out of ddI. Patient care would be enhanced, given the issues of multiple toxicities, monitoring, drug interactions, inconvenience, and virologic efficacy which have been described (Table 1). There would also be discernible program-level benefits. Beyond the cost savings, the simplification of the formulary would lead to a more streamlined supply chain process. Attention could then be focused on the ARVs, including new drug classes and improved FDCs, which bring real value to ART programs and to people living with HIV.

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References

1. Food and Drug Administration. [accessed 6 February 2014] Revised label for Videx EC (didanosine). http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021183s025lbl.pdf
2. World Health Organization. Scaling up antiretroviral therapy in resource-limited settings – guidelines for a public health approach. World Health Organization; Geneva: 2002.

3. World Health Organization. Scaling up antiretroviral therapy in resource-limited settings – treatment guidelines for a public health approach. World Health Organization; Geneva: 2003. revision
4. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents – recommendations for a public health approach. World Health Organization; Geneva: 2006. revision
5. World Health Organization. Antiretroviral therapy of HIV infection in infants and children – recommendations for a public health approach. World Health Organization; Geneva: 2006. revision
6. World Health Organization. Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents. World Health Organization; Geneva: 2009.
7. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents – recommendations for a public health approach. World Health Organization; Geneva: 2010. revision
8. World Health Organization. Antiretroviral therapy for HIV infection in infants and children: towards universal access – recommendations for a public health approach. World Health Organization; Geneva: 2010. revision
9. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. World Health Organization; Geneva: 2013.
10. Fox Z, Dragsted UB, Gerstoft J, et al. A randomized trial to evaluate continuation versus discontinuation of lamivudine in individuals failing a lamivudine-containing regimen: the COLATE trial. Antivir Ther. 2006; 11:761–770. [PubMed: 17310820]
11. Sproat M, Pozniak AL, Peeters M, et al. The influence of the M184V mutation in HIV-1 reverse transcriptase on the virological outcome of highly active antiretroviral therapy regimens with or without didanosine. Antivir Ther. 2005; 10:357–361. [PubMed: 15865231]
12. Hull, M.; Moore, D.; Harris, M., et al. A lamivudine (3TC)-based backbone in conjunction with a boosted protease inhibitor (PI) is sufficient to achieve virologic suppression in the presence of M184V mutations. 49th interscience conference on antimicrobial agents and chemotherapy; San Francisco. 2009;
13. The Global Fund to Fight AIDS, Tuberculosis and Malaria. [accessed 6 February 2014] Price and Quality Reporting (PQR) website. http://bi.theglobalfund.org/analytics/saw.dll?Dashboard
14. Supply Chain Management System (SCMS). [accessed 6 February 2014] Antiretroviral pricing website. http://scms.pfscm.org/scms/working/procurement/pastorders
15. Apostolova N, Blas-García A, Esplugues JV. Mitochondrial interference by anti-HIV drugs: mechanisms beyond Pol-γ inhibition. Trends Pharmacol Sci. 2011; 32:715–725. [PubMed: 21899897]
16. Kovari H, Ledergerber B, Peter U, et al. Association of noncirrhotic portal hypertension in HIV-infected persons and antiretroviral therapy with didanosine: a nested case-control study. Clin Infect Dis. 2009; 49:626–635. [PubMed: 19589079]
17. Schouten JN, Van der Ende ME, Koëter T, et al. Risk factors and outcome of HIV-associated idiopathic noncirrhotic portal hypertension. Aliment Pharmacol Ther. 2012; 36:875–885. [PubMed: 22971050]
18. Chang HM, Tsai HC, Lee SS, et al. Noncirrhotic portal hypertension associated with didanosine: a case report and literature review. Jpn J Infect Dis. 2012; 65:61–65. [PubMed: 22274160]
19. Prosperi MC, Fabbiani M, Fanti I, et al. Predictors of first-line antiretroviral therapy discontinuation due to drug-related adverse events in HIV-infected patients: a retrospective cohort study. BMC Infect Dis. 2012; 12:296. [PubMed: 23145925]
20. Gabrielian A, MacCumber MM, Kukuyev A, et al. Didanosine-associated retinal toxicity in adults infected with human immunodeficiency virus. JAMA Ophthalmol. 2013; 131:255–259. [PubMed: 23411900]
21. Food and Drug Administration. [accessed 6 February 2014] Medication Guide for Videx EC (didanosine). http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021183s025MG.pdf
22. Hamkar R, Mohraz M, Lorestani S, et al. Assessing sub-type and drug-resistance-associated mutations among antiretroviral-treated HIV-infected patients. AIDS. 2010; 24(Suppl 2):S85–91. [PubMed: 20610954]
23. Waters L, Nelson M, Mandalia S, et al. The risks and incidence of K65R and L74V mutations and subsequent virologic responses. Clin Infect Dis. 2008; 46:96–100. [PubMed: 18171220]

24. Steegen K, Levin L, Ketseoglou I, et al. High-level cross-resistance to didanosine observed in South African children failing an abacavir- or stavudine-based 1st-Line regimen. PLoS One. 2014; 9:e97067. [PubMed: 24816790]

25. Houssaini A, Assoumou L, Miller V, et al. Scoring methods for building genotypic scores: an application to didanosine resistance in a large derivation set. PLoS One. 2013; 8:e59014. [PubMed: 23555613]

26. Iversen AK, Shafer RW, Wehrly K, et al. Multidrug-resistant human immunodeficiency virus type 1 strains resulting from combination antiretroviral therapy. J Virol. 1996; 70:1086–1090. [PubMed: 8551567]

27. Cunha, R.; Abreu, C.; Mabombo, V., et al. In vitro accumulation of drug resistance mutations in subtype B and C chimeric infectious clones selected with tenofovir and didanosine. Conference on retroviruses and opportunistic infections; Atlanta. 2013;

28. Cho YK, Kim B, Kim JE, et al. First report on a T69-ins insertion in CRF06-cpx HIV-1. AIDS Res Hum Retroviruses. 2013; 29:1079–1084. [PubMed: 23506217]

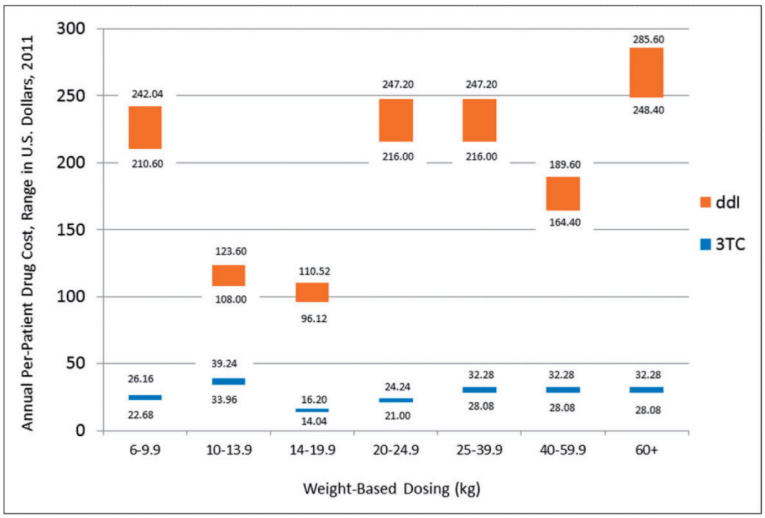

Figure 1.

Annual per-patient costs of didanosine and laminvudine through Global Fund Price & Quality Reporting System, by weight-adjusted dosing.

Table 1

Comparative analysis: didanosine versus lamivudine.

Attributes	Didanosine	Lamivudine
Use in patients starting new regimens	Not recommended by WHO	Recommended by WHO
Toxicity profile	High	Low
Recommended monitoring	Complex (pancreatic enzymes; retinal exams)	None
Drug interactions	Many	Few
Complications with ethanol	Yes (concurrent use increases risk of pancreatitis)	No
Timing of dosage	Must be separated from food and other ARVs	Able to take concurrent with food and other ARVs
Fixed-dose combinations	None available	Several available
Efficacy in second-line due to mutations	Variable; L74V frequent; may select for multinucleoside mutations	Variable; M184V usually present; may select for decreased viral fitness
Cost	High	Low
Supply chain	Complex; high number of formulations	Streamlined